Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

## **IN THE CLAIMS**

Please amend the claims as follows:

## 1-172. (Canceled).

173. (Currently Amended) A therapeutic method for treating a cardiovascular or vascular indication characterized by a decreased lumen diameter comprising locally administering to a human identified as being at risk of or afflicted with said cardiovascular or vascular indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):

$$(R^1)(R^2)N(CH_2)_2O$$

$$(Z)$$

$$R^3$$

$$R^5$$

$$R^4$$

wherein Z is C=O or a covalent bond; Y is H or  $O(C_1-C_4)$ alkyl,  $R^1$  and  $R^2$  are individually  $(C_1-C_4)$ alkyl or together with N are a saturated heterocyclic group,  $R^3$  is ethyl or chloroethyl,  $R^4$  is H,  $R^5$  is I,  $O(C_1-C_4)$ alkyl or H and  $R^6$  is I,  $O(C_1-C_4)$ alkyl or H with the proviso that when  $R^4$ ,  $R^5$ , and  $R^6$  are H,  $R^3$  is not ethyl; or a pharmaceutically acceptable salt thereof.

174. (Previously Presented) The method of claim 173 wherein the cytostatic dose is effective to increase the level of TGF-beta so as to decrease lesion formation or development, decrease

Serial Number:09/754,775 Dkt: 295.009US3

Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

lipid accumulation, increase plaque stability, maintain or increase vessel lumen diameter, or any combination thereof.

- 175. (Previously Presented) The method of claim 173 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, toremifene, or a pharmaceutically acceptable salt thereof.
- 176. (Previously Presented) The method of claim 173 wherein the compound of formula (I) is idoxifene or a pharmaceutically acceptable salt thereof.
- 177. (Previously Presented) The method of claim 173 wherein the compound of formula (I) is toremifene or a pharmaceutically acceptable salt thereof.
- 178. (Canceled).
- 179. (Previously Presented) The method of claim 173 wherein the compound of formula (I) is administered via a sustained release dosage form.
- 180. (Previously Presented) The method of claim 173 wherein the administration is localized at the site of vascular trauma.
- 181. (Previously Presented) The method of claim 173 wherein the compound directly or indirectly increases the level of active TGF-beta.
- 182. (Currently Amended) A therapeutic method of increasing the level of TGF-beta in a diabetic mammal at risk of or afflicted with a cardiovascular or vascular indication characterized by a decreased lumen vessel diameter, comprising administering to a diabetic mammal at risk of or afflicted with [[said]] a cardiovascular or vascular indication an effective amount of a compound of formula (I):

Serial Number:09/754,775 Dkt: 295.009US3

Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

$$(R^1)(R^2)N(CH_2)_2O$$

$$(Z)$$

$$R^3$$

$$R^5$$

$$R^6$$

$$R^4$$

wherein Z is C=O or a covalent bond; Y is H or  $O(C_1-C_4)$ alkyl,  $R^1$  and  $R^2$  are individually  $(C_1-C_4)$ alkyl or together with N are a saturated heterocyclic group,  $R^3$  is ethyl or chloroethyl,  $R^4$  is H or together with  $R^3$  is  $-CH_2-CH_2$ - or -S-, R5 is I, OH,  $O(C_1-C_4)$ alkyl or H and  $R^6$  is I,  $O(C_1-C_4)$ alkyl or H with the proviso that when  $R^4$ ,  $R^5$ , and  $R^6$  are H,  $R^3$  is not ethyl; or a pharmaceutically acceptable salt thereof.

- 183. (Previously Presented) The method of claim 182 wherein the increase in TGF-beta reduces diabetic retinopathy.
- 184. (Previously Presented) The method of claim 182 wherein the mammal is a human.
- 185. (Previously Presented) The method of claim 184 wherein the diabetic has retinopathy.
- 186. (Previously Presented) The method of claim 182 wherein the compound indirectly or directly increases the level of active TGF-beta in vascular tissue.
- 187. (Previously Presented) The method of claim 182 wherein the compound is a TGF-beta production stimulator.
- 188. (Previously Presented) The method of claim 182 wherein the compound is a TGF-beta activator.

Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

189. (Previously Presented) The method of claim 182 wherein the compound increases the production of TGF-beta mRNA.

- 190. (Previously Presented) The method of claim 182 wherein the compound increases the cleavage of the latent form of TGF-beta.
- 191. (Previously Presented) The method of claim 182 wherein the compound increases the bioavailability of TGF-beta.
- 192. (Previously Presented) The method of claim 182 wherein the compound is idoxifene or a pharmaceutically acceptable salt thereof.
- 193. (Previously Presented) The method of claim 182 wherein the compound is toremifene or a pharmaceutically acceptable salt thereof.
- 194. (Previously Presented) The method of claim 182 wherein the compound is droloxifene or a pharmaceutically acceptable salt thereof.
- 195. (Canceled).
- 196. (Previously Presented) The method of claim 173 or 182 wherein the compound forms cellular DNA adducts at level which is reduced relative to DNA adduct formation by tamoxifen.
- 197. (Previously Presented) The method of claim 173 or 182 wherein the compound has estrogenic activity which is reduced relative to the estrogenic activity of tamoxifen.
- 198. (Previously Presented) The method of claim 173 or 182 wherein the compound does not form cellular DNA adducts.

Serial Number:09/754,775 Dkt: 295.009US3

Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

199. (Previously Presented) The method of claim 173 or 182 wherein the compound has no estrogenic activity.

200. (Currently Amended) A method of increasing the level of TGF-beta in a human identified as being afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, comprising selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering to a human identified as being afflicted with a cardiovascular indication an effective amount of the agent agent.

201. (Canceled).

202. (Previously Presented) The method of claim 200 wherein the agent is idoxifene or a pharmaceutically acceptable salt thereof.

203. (Previously Presented) The method of claim 200 wherein the agent is toremifene or a pharmaceutically acceptable salt thereof.

204. (Canceled).

205. (Previously Presented) The method of claim 173, 182, or 200 wherein the administration increases the level of latent TGF-beta relative to the level of latent TGF-beta prior to said administration.

206. (Previously Presented) The method of claim 173, 182, or 200 wherein the administration increases the level of active TGF-beta relative to the level of active TGF-beta prior to said administration.

207-230. (Canceled).

Filing Date: January 4, 2001

Title: PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES

231. (Currently Amended) A therapeutic method for treating a condition selected from the group consisting of arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, and retinopathy, comprising administering to a mammal afflicted with said condition, an effective amount of a compound of formula (I):

$$(R^1)(R^2)N(CH_2)_2O$$

$$(Z)$$

$$R^3$$

$$R^5$$

$$R^6$$

$$R^4$$

wherein Z is C=O or a covalent bond; Y is H or  $O(C_1-C_4)$ alkyl,  $R^1$  and  $R^2$  are individually  $(C_1-C_4)$ alkyl or together with N are a saturated heterocyclic group,  $R^3$  is ethyl or chloroethyl,  $R^4$  is H,  $R^5$  is I,  $O(C_1-C_4)$ alkyl or H and  $R^6$  is I,  $O(C_1C_4)$ alkyl or H with the proviso that when  $R^4$ ,  $R^5$ , and  $R^6$  are H,  $R^3$  is not ethyl; or a pharmaceutically acceptable salt thereof.

232-233. (Canceled).

234. (Previously Presented) The method of claim 173, 182, or 231 wherein R<sup>5</sup> or R<sup>6</sup> is I.